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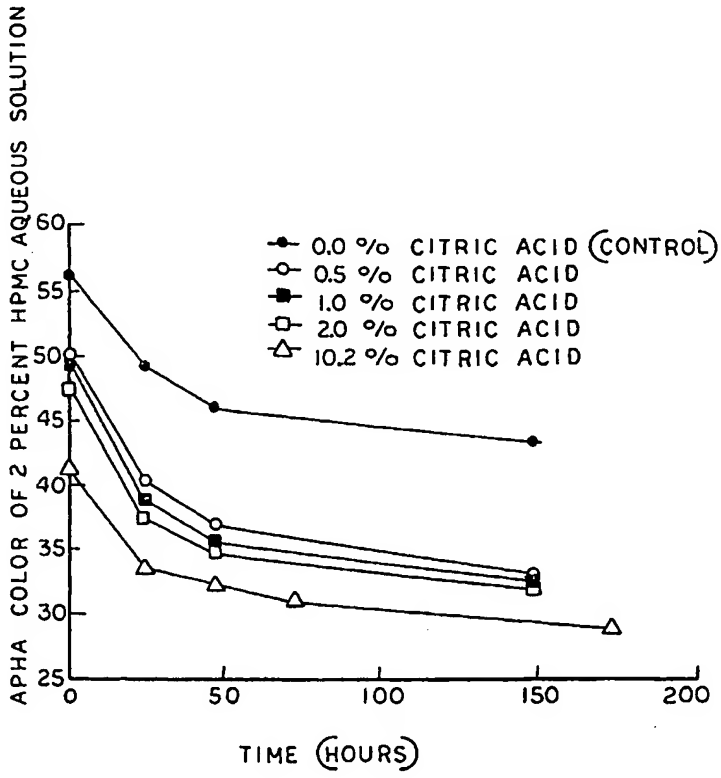
(54) Title: PROCESS FOR MAKING CELLULOSE ETHER CAPSULES WITH ORGANIC ACIDS

(57) Abstract

Disclosed is a process for making cellulose ether capsules from a cellulose ether composition having a pH of about 5 or less. The process can provide reduced drying time and/or temperature, reduced yellowing or discoloration in end product capsules, enhanced antimicrobial resistance, and enhanced dissolution rates. Also disclosed is a cellulose ether composition having a pH of about 5 or less.



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PROCESS FOR MAKING CELLULOSE ETHER CAPSULES WITH ORGANIC ACIDS

The present invention relates to an improved process for making cellulose ether capsules. The process employs a cellulose ether composition having an organic acid therein. The capsules are useful in pharmaceutical applications.

Cellulose ethers are commonly employed commercially to form capsules which are adapted to contain and orally deliver pharmaceutical agents and medicaments. Preferred cellulose ethers for such applications are methylcellulose and hydroxypropylmethylcellulose.

A problem in manufacturing pharmaceutical capsules is the lengthy time and the elevated temperatures required to effect drying of aqueous cellulose ether solutions in forming capsule caps and bodies. Reducing drying time reduces capsule manufacturing time. Reducing drying temperatures levels reduces energy costs and allows process operating conditions to be broadened.

Another problem sometimes observed in manufacturing pharmaceutical capsules is yellowing or discoloration in the end product. Such yellowing or discoloration is most easily observed in transparent capsules.

Another problem sometimes observed in manufacturing pharmaceutical capsules is microbial contamination. Aqueous cellulose ether solutions from which capsules are made are susceptible to contamination.

Another problem sometimes observed in end product pharmaceutical capsules is retarded dissolution rates. Capsules may not dissolve fast enough in the stomach.

It would be desirable to have a process for manufacturing pharmaceutical capsules wherein drying time and/or temperature can be reduced. It would also be desirable to have a process wherein yellowing or discoloration can be reduced in end product capsules. It would also be desirable to have a process for manufacturing pharmaceutical capsules wherein antimicrobial resistance can be enhanced. It would also be desirable to have pharmaceutical capsules that dissolve faster.

According to the present invention, there is a process for making cellulose ether capsules from a cellulose ether composition having a cellulose ether and about 0.1 to about 15 weight percent of an organic acid based upon the total weight of the cellulose ether and the organic acid. The composition has a pH of about 5 or less. The composition is dissolved in water to form a dip coating solution. Metal pins are dipped into the coating solution. The solution is allowed to thermally gel and subsequently dry on the pins to form thin films of dried cellulose ether composition around the pins. The thin films take the form of caps and/or bodies of two-piece hard shell capsules which are then removed from the pins. The caps and/or bodies can subsequently be mated to form whole capsules. Both hot pin/cold solution and cold pin/hot solution processes are possible.

Further according to the present invention, there is a capsule of a cellulose ether composition comprising a cellulose ether composition having 0.1 to 15 percent of an organic acid based upon the total weight of the cellulose ether and the organic acid.

In the present invention, it was discovered that the regulation of pH of a cellulose ether composition in a process for making pharmaceutical capsules yielded several surprising and unexpected advantages. One advantage was an enhancement in

drying properties. Drying time and/or temperature can be reduced. Another advantage is a reduction in yellowing or discoloration observed in end product capsules. Another advantage is enhancement of the antimicrobial resistance of the capsules. Yet another advantage is enhanced dissolution rates for the capsules. The disclosed advantages can be afforded to varying degrees depending upon the level of acid content and pH employed.

Acidic content can be regulated by any know means such as retention of acidic content from manufacture and/or external addition of acid to a cellulose ether composition.

The acid is preferably present at an amount sufficient to provide a cellulose ether composition of a pH of about 6 or less, more preferably about 5 or less, and most preferably about 4 or less on a conventional pH logarithmic scale of 0 to 14. Acidic content will vary according to the strength of the acid and will typically range from 0.1 to 15 percent and preferably from 0.1 to 5.0 percent based upon the total weight of the cellulose ether and the acid.

Useful organic acids include but are not limited to citric acid, ethylenediaminetetraacetic acid, acetic acid, boric acid, gluconic acid, lactic acid, tartaric acid. A most preferred organic acid is citric acid.

Control of pH of a cellulose ether composition by addition of an organic acid is advantageous compared to control by manipulation of residual acid content remaining in a cellulose ether after manufacture. In conventional manufacturing processes for making low molecular weight cellulose ethers useful in pharmaceutical capsules, a higher molecular weight cellulose ether is depolymerized to the lower molecular weight cellulose ether by acid-catalyzed hydrolysis, usually by exposure to a strong inorganic acid such as hydrogen chloride

or hydrochloric acid. After the desired degree of depolymerization is achieved, hydrolysis is halted by neutralization of the acid with an alkaline or basic compound such as sodium bicarbonate. Residual acid content can be maintained in the end product cellulose ether by neutralizing only a portion of the catalyzing acid. Although lower pH can be achieved by maintaining a portion of the catalyzing acid, the end product cellulose ether containing it can be physically unstable since the cellulose ether continues to depolymerize. In the present, the advantage of lower pH is afforded while stability problems are avoided by adding a quantity of organic acid to the cellulose ether composition. The organic acid is not observed to significantly impact the physical stability of the cellulose ether.

Cellulose ether capsules are typically manufactured by dipping hot metal pins or bars in a cold, aqueous cellulose ether dip coating solution. The solution thermally gels on the pins and water evaporates during a drying step to form thin film layers of dried cellulose ether around the hot pins. The thin films take the form of caps and bodies, which are then removed from the pins. Caps are mated with bodies to form capsules. Analogous processes exist wherein cold pins are dipped in a hot, aqueous cellulose ether solution. Both processes are within the scope of the present invention Processes for making capsules are seen in U.S. Patent Nos. 3,617,588; 4,001,211; 4,917,885; and 5,756,036.

Useful cellulose ethers include the following: methylcellulose (MC), hydroxyethylmethylcellulose (HEMC), hydroxypropylmethylcellulose (HPMC), hydroxyethyl-methylcellulose (HEMC), ethylhydroxyethylcellulose (EHEC) and hydroxybutylmethylcellulose (HBMC). A particularly useful cellulose ether in making capsules is hydroxypropylmethylcellulose.

Cellulose ethers useful in the present invention typically have molecular weights such that a two percent aqueous solution at 20°C has a viscosity of about 100 cP or less, preferably 3 to 100 cP, and most preferably 3 to 15 cP in a two percent aqueous solution at 20°C.

Useful teachings relating to the manufacture of cellulose ethers are seen in the following: U.S. Patents 3,391,135; 4,419,510; 4,456,751; 4,477,657; 4,661,589; 5,476,668; and U.S. Serial No. 09/203,324, filed December 1, 1998.

The cellulose ether composition is preferably substantially free of hydrocolloids other than cellulose ethers. Representative hydrocolloids are disclosed in WO 98/27151.

The cellulose ether composition may be used in other pharmaceutical applications such as tablet coatings and exipients for pharmaceutical agents and medicaments in capsules and tablets.

EXAMPLES

Cellulose ether compositions with and without an organic acid were prepared and examined or tested for color.

Example 1

Aqueous cellulose ether compositions were prepared by dispersing 2 weight percent Methocel™ F4 brand hydroxypropylmethylcellulose (HPMC) in water based upon the total weight of the HPMC and water. The HPMC has a hydroxypropyl content of 5.8 percent and a methoxy content of 28.9 percent based upon the weight of the HPMC. The HPMC has a viscosity of 4 cP in a 2 percent aqueous solution at 20°C.

Citric acid was added to compositions at loadings of 0.5 percent, 1.0 percent, 2 percent, and 10.2 percent based upon the total weight of the citric acid, HPMC, and water. One cellulose ether composition was prepared without citric acid to serve as a control. The solutions were allowed to sit for 3 days to substantially eliminate entrained air within the solutions.

The solutions were tested for color in a colorimeter Color was characterized by the APHA (American Public Health Association) water color standard. The standard is seen in American Public Health Association, *Standard Methods for the Examination of Water and Wastewater*, 14th Edition, pp. 64-66.

Results are shown in the Figure. The results show a clear correlation between reduced color and the presence of citric acid. All solutions with citric acid showed reduced color relative to the control (no citric acid). Color decreased as citric acid content increased.

Example 2

Aqueous cellulose ether compositions were prepared by dispersing 15 weight percent Methocel F4 brand hydroxypropylmethylcellulose (HPMC) in water based upon the total weight of the HPMC and water. The HPMC has a hydroxypropyl content of 5.8 percent and a methoxy content of 28.9 percent based upon the weight of the HPMC. The HPMC has a viscosity of 4 cP in a 2 percent aqueous solution at 20°C. Citric acid was added to compositions at loadings of 0.1 percent, 1.0 percent, and 15 percent based upon the total weight of the citric acid, HPMC, and water. One cellulose ether composition was prepared without citric acid to serve as a control. The solutions were allowed to sit for 3 days to substantially eliminate entrained air within the solutions.

The solutions were examined for color with the naked eye. The results show a clear correlation between reduced color and the presence of citric acid. The solutions ranged in color from brown for the control composition to light pale yellow for the solution with 15 percent citric acid. All solutions with citric acid showed reduced color (less brown color) relative to the control (no citric acid).

While embodiments of the present capsule and the process for making it have been shown with regard to specific details, it will be appreciated that the present invention may be modified while still being fairly within the scope of the novel teachings and principles set forth herein.

WHAT IS CLAIMED IS:

1. A pharmaceutical capsule, the capsule comprising a cellulose ether composition, the composition comprising a cellulose ether and an organic acid, the organic acid being present at from 0.1 to 15 weight percent based upon the total weight of the cellulose ether and the organic acid.

2. The capsule of Claim 1, wherein the cellulose ether composition comprises 0.1 to 5.0 percent organic acid based upon the total weight of the cellulose ether and the organic acid.

3. The capsule of Claim 1, the cellulose ether being hydroxypropylmethylcellulose.

4. The capsule of Claim 1, wherein the viscosity of the cellulose ether is 3 to 15 cP.

5. The capsule of Claim 1, wherein the cellulose ether composition comprises an organic acid.

6. The capsule of Claim 1, wherein the organic acid is present at an amount sufficient to provide a cellulose ether composition of a pH of about 6 or less.

7. The capsule of Claim 1, wherein the organic acid is present at an amount sufficient to provide a cellulose ether composition of a pH of about 5 or less.

8. The capsule of Claim 1, wherein the organic acid is present at an amount sufficient to provide a cellulose ether composition of a pH of about 4 or less.

9. The capsule of Claim 1, the wherein the cellulose ether composition comprises an organic acid at from 0.1 to 5.0 percent based upon the total weight of the cellulose ether and the organic acid, the cellulose ether being hydroxypropylmethylcellulose, the viscosity of the hydroxypropylmethylcellulose being 3 to 15 cP in a 2 percent aqueous solution at 20°C, the cellulose ether composition having a pH of about 6 or less.

10. The capsule of Claim 9, wherein the organic acid is present at an amount sufficient to provide a cellulose ether composition of a pH of about 4 or less.

11. The capsule of Claim 1, wherein the cellulose ether composition is substantially free of hydrocolloid ethers other than cellulose ethers.

12. A process for making pharmaceutical capsules, the process comprising: a) providing a cellulose ether composition comprising a cellulose ether and an acid wherein the acid is present at 0.1 to 15 weight percent based upon the total weight of the cellulose ether and the organic acid; b) dissolving the cellulose ether composition in water to form a dip coating solution; c) dipping metal pins into the coating solution; d) removing the pins from the coating solution; e) allowing the solution to thermally gel and subsequently dry on the surfaces of the pins to form caps and/or bodies; and f) removing the caps and/or bodies from the metal pins.

13. The process of Claim 12, wherein the cellulose ether composition comprises 0.1 to 5.0 percent organic acid

based upon the total weight of the cellulose ether and the acid.

14. The process of Claim 12, the cellulose ether being hydroxypropylmethylcellulose.

15. The process of Claim 12, wherein the viscosity of the cellulose ether is 3 to 15 cP.

16. The process of Claim 12, wherein the organic acid organic acid is present at an amount sufficient to provide the cellulose ether composition with a pH of about 6 or less.

17. The process of Claim 12, wherein the organic acid is present at an amount sufficient to provide the cellulose ether composition with a pH of about 5 or less.

18. The process of Claim 12, wherein the organic acid is present at amount sufficient to provide the cellulose ether composition with a pH of about 4 or less.

19. The process of Claim 12, the wherein the cellulose ether composition comprises an organic acid at from about 0.1 to about 5.0 percent based upon the total weight of the cellulose ether and the organic acid, the cellulose ether being hydroxypropylmethylcellulose, the viscosity of the hydroxypropylmethylcellulose being 3 to 15 cP in a 2 percent aqueous solution at 20°C, the cellulose ether composition having a pH of about 6 or less.

20. The process of Claim 12, wherein the cellulose ether composition is substantially free of hydrocolloid ethers other than cellulose ethers.

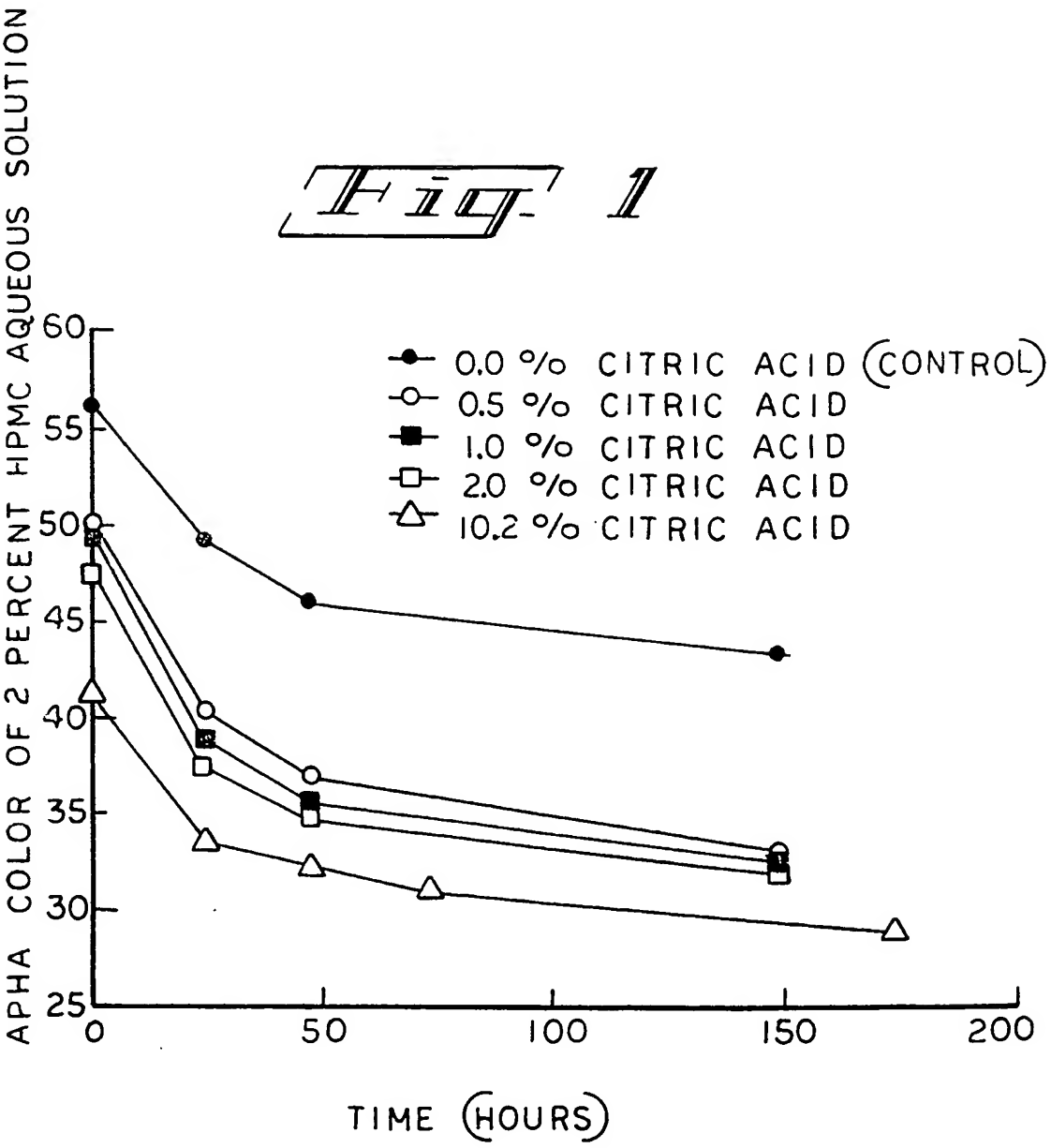
21. The process of Claim 12, wherein the process is a hot pin/cold solution process.

22. The process of Claim 19, wherein the process is a hot pin/cold solution process.

23. The process of Claim 12, wherein the process is a cold pin/hot solution process.

24. The process of Claim 19, wherein the process is a cold pin/hot solution process.

Fig. 1


APHA COLOR OF 2 PERCENT HPMC AQUEOUS SOLUTION
60
55
50
45
40
35
30
25
0
50
100
150
200
TIME (HOURS)
0.0 % CITRIC ACID (CONTROL)
0.5 % CITRIC ACID
1.0 % CITRIC ACID
2.0 % CITRIC ACID
10.2 % CITRIC ACID

INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/US 00/12612

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

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Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 757 173 A (WARNER LAMBERT) 19 June 1998 (1998-06-19) claims 1,2,4,5,11,12,14	1-24
X	EP 0 357 369 A (PFIZER) 7 March 1990 (1990-03-07) column 2, line 15 - line 37	1,2

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter inal Application No
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